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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,822	04/24/2001	Thorvald Eelco Wallaart	702-010272	3747

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,822	WALLAART ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-86* is/are pending in the application.

4a) Of the above claim(s) *66-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *43-65 and 75-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. ***Election***

Applicant's election with traverse of Group I, claims 43-65 and 75-86, filed May 25, 2004 is acknowledged. In particular, the traversal is on the ground(s) that Group I and II contains claims that directly or indirectly recite DNA of SEQ ID NO: 13 that encodes a polypeptide having the biological activity of amorphadiene synthase (SEQ ID NO: 14); and Groups III and IV contain claims that recite methods for preparing amorphadiene or arteminisin that directly or indirectly use DNA of SEQ ID NO: 13. Thus the distinguishing feature of all the claims is the DNA of SEQ ID NO: 13.

This is not found persuasive because the DNA and protein are structurally and chemically distinct molecules, each requiring separate sequence searches. Contrary to Applicants' claim, the special technical feature of group I is the DNA of SEQ ID NO: 13 and is not shared by group II having the special technical feature of the polypeptide of SEQ ID NO: 14. Indeed the two are related in that the DNA of SEQ ID NO: 13 codes for the polypeptide of SEQ ID NO: 14, they are distinct inventions because the protein product can be made by other and materially distinct processes, such as purification from the natural source. Further, DNA can be used for processes other than the

production of protein, such as nucleic acid hybridization assays.

As far the method claims are concerned, claims 69 & 71-74 (Group IV), reciting DNA of SEQ ID NO: 13, will be rejoined with the instantly elected claims subject to the conditions of following rejoinder, which was indicated in the prior Office Action.

> ***Rejoinder:*** The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicants further argue that all the four groups are classified in the same class and two of the four groups share the same sub-class. Applicants further contend that even those claims that are not classified in the same sub-class would not place an undue burden on the Examiner, because based on the fact that the special technical feature of all the claims is SEQ ID

NO: 13, examination of claims in one group is believed to be coextensive with the examination of claims of the other groups.

This is not found persuasive because (1) the special technical feature of all the claims is not SEQ ID NO: 13 and (2) depending upon the restricted group (I or II or III or IV) being examined, additional classes/subclasses will have to be searched. For example, Group I claims, drawn to DNA of SEQ ID NO: 13 encoding a protein having the enzymatic activity of amorpha-4, 11-diene synthase, vector , host cell and a method of making the protein, will involve searching for additional class 536 & subclass 23.2 for DNA encoding the enzyme; apart from the respective DNA/protein sequence(s) data bases search in question, depending upon the elected class. The searches are not coextensive, because searching for DNA sequence will not automatically obtain results for the polypeptide sequence; as searching for one class/subclass will not gather results for other classes/subclasses. This additional searching as explained above would therefore involve undue burden to the Examiner. The requirement is still deemed proper and is therefore made FINAL.

2. **Claims withdrawn** :

Claims 66-74 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No.

3. Claims 43-65 and 75-86 are under consideration in this examination.

4. ***Priority***

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in European patent Office on August 27, 1998. The foreign priority paper(s) have been scanned with the prior art documents (Information Disclosure Statement).

5. ***Sequence Rules***

The instant specification, for example - claims 44-46 & 85-86, recite Fig. 12, that is encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), but fails to comply with the requirements. According to 37 CFR 1.821-825, every disclosed amino acid sequence of four or more residues or 10 or more nucleotides must be identified by a SEQ ID NO. The amino acid sequences presented do not have SEQ ID NOs. In order to comply with the sequence rules Applicants must identify these sequences by providing SEQ ID NO:, and where required provide a new version of the sequence listing and disk.

As per preliminary amendment filed 05.05.2003, Figures 8, 10 and 12 have been identified by SEQ ID Nos. However, it is

noted that claims 44-46 & 85-86 recite Fig. 12., instead of sequence ID Nos., which is also not is compliance with the sequence rules. Replacing Fig. 12 with the appropriate SEQ ID NO: is required.

Specification

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. ***35 U.S.C.§ 112, first paragraph (Written Description)***

Claims 43, 47-65 & 75-86 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 43, 47-65 & 75-86 recite an 'isolated DNA sequence having the biological activity of amorpha-4,11-diene synthase' (claim 43); or wherein, the DNA sequence is obtained from a plant (claim 47); or vector, host cell, DNA construct, method of making amorpha-4,11-diene synthase recombinantly (claims 48-65 & 75-86) using the DNA from source as defined by claims 43 & 47.

The specification, however, only provides a single representative species from *Artemisia annua* (sweet wormwood) of SEQ ID NO : 13. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species in order to make a polypeptide having the synthase activity from any source, based upon the single source that is described. The specification fails to describe additional representative species of these amorpha-4,11-diene synthases by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Given this lack of additional representative species, of the DNA of SEQ ID NO : 13 and the associated activity [amorpha-4,11-diene synthase] encoded by these innumerable DNA molecules, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Therefore, the written description requirement is not satisfied.

9. ***35 U.S.C.§ 112, first paragraph (Enablement)***

Claims 43-45, 47-65 and 75-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA sequence of SEQ ID NO : 13 encoding an amorpha-4,11-diene synthase of SEQ ID NO : 14, does not reasonably provide enablement for a DNA from any source or a DNA from any plant encoding an amorpha-4,11-diene synthase; or a DNA sequence that is 70%, 80%, 90% or 95% identical to SEQ ID NO : 13 [or Figure 12] and encoding a protein having amorpha-4,11-diene synthase activity.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))[*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the

breadth of the claim. The factors most relevant to this rejection are [the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

The specification provides guidance and examples for making an isolated DNA sequence comprising SEQ ID NO : 13 and the encoded polypeptide sequence of SEQ ID NO: 14 [amorpha-4,11-diene synthase]. However, the specification does not teach the specific structural/catalytic amino acids and the structural motifs essential for protein activity/function which cannot be altered. The state of the art as exemplified by Attwood et al. [Comput. Chem. 2001, col. 54(4), pp. 329-39] is such that "..we do not fully understand the rules of protein folding, so we cannot predict protein structure; and we cannot invariably diagnose protein function, given the knowledge only of its sequence or structure in isolation" (see abstract and the entire publication). Further Ponting [Brief. Bioinform. March 2001, Vol. 2(1), pp. 19-29] states that "...predicting function by homology is a qualitative, rather than quantitative process and requires particular care to be taken, due attention should be paid to all available clues to function, including orthologue identification, conservation of particular residue types, and

the co-occurrence of domain in proteins" (see abstract and the entire publication).

The standard of meeting enablement requirement is whether one of skill in the art can make the invention without undue experimentation. The amount of experimentation to make the claimed polynucleotide is enormous and entails selecting specific nucleotides to change (deletion, insertion, substitution or combination thereof) in a polynucleotide to make a claimed polynucleotide and determining by assays whether the polypeptide has activity. The specification does not provide guidance with respect to the specific structural/catalytic amino acids and the structural motifs essential for enzyme structure/function which must be preserved. Thus, searching for the specific nucleotides to change (deletion, insertion, substitution or combination thereof) in a polynucleotide to make polynucleotide that is at least 70%, 80%, 90% or 95% identical to a polynucleotide comprising nucleotide sequence of SEQ ID NO : 13 is well outside the realm of routine experimentation and predictability in the art of success in determining whether the resulting polypeptide has activity (same, other or none) is extremely low since no structural motifs essential for enzyme structure and activity/function which must be preserved.

Applicants' attention is specially drawn to Accession No. AF327526 [Liu et al, 2001, not prior art], a DNA sequence encoding sesquiterpene cyclase [CN : Farnesyl pyrophosphate cyclase] and is 98.6% identical to Applicants' SEQ ID NO: 13. [see the enclosed sequence search alignment]. As can be seen, a difference of 0.4% between Accession No. AF327526 and Applicants' SEQ ID NO: 13, results in the DNA encoding a totally different protein having different enzyme activity. Therefore, modifying a DNA sequence encoding amorpha-4,11-diene synthase between 5 and 30% will be highly unpredictable, and based upon the works of Liu et al., most likely will not produce a DNA capable of encoding a protein having amorpha-4,11-diene synthase activity.

Further, the specification does not support the broad scope of the claims which encompass all DNA sequences encoding amorpha-4,11-diene synthase from any source, because the specification only teaches a single DNA species capable of encoding amorpha-4,11-diene synthase from *Artimisia*. The prior art is silent about DNA from other plants, microorganisms, etc., which are capable of encoding amorpha-4,11-diene synthase.

Therefore, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific catalytic amino acids and structural motifs

essential for activity/function which must be preserved and/or other DNA sequences encoding amorpha-4,11-diene synthase, in order to provide guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. Without such a guidance, the experimentation left to those skilled in the art is undue.

10. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 43-65 and 75-86 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "biological activity" in claims 43-44, is used by the claim to mean "enzyme activity", while the

accepted meaning include "all biological activities, which may be binding, immunological, enzymatic, etc." The term is indefinite because the specification does not clearly redefine the term. A detailed explanation is as follows :

The biological activity of the enzyme amorphadiene synthase relates to the conversion of the general precursor farnesyl pyrophosphate (FPP) into the specific artemisinin precursor amorpha-4,11-diene, which, in A. annua, is further converted to artemisinin. [Instant specification, page 4, 4th paragraph].

Applicants' specification although defines the phrase 'biological activity' as equivalent to 'enzyme activity', however, the art accepted or general meaning of 'biological activity' would include other activities, such as 'binding activity', 'antigenic' or 'immunological activity', therefore, applicant definition is narrow and unclear.

It is suggested to use 'enzymatic activity' instead of 'biological activity' to overcome this rejection.

Claims 45-65 and 75-86 are included in the rejection for failing to correct the defect present in the base claim(s).

11. Claims 44-46 and 85-86 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 44-46 & 85-86 refer to Fig. 12 and DNA sequence. The claims are unclear because Fig. 12 shows both the DNA and the encoded amino acid sequence. Reference to SEQ ID NO: 13 instead of 'Fig. 12' is suggested to overcome this rejection.

12. Claims 56-57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56, line 2, recites 'can be induced by elicitation'. The claim is unclear and indefinite because 'induction' and 'elicitation' mean the same or are synonymous. Using one or the other will overcome this rejection.

Claim 57 is included in the rejection for failing to correct the defect present in the base claim(s).

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (571) 272-0940. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group in the Technology Center is 703 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 571 272-1600.

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